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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/647,330	02/23/2001	William Osmond Charles Michael Cookson		5707

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,330	COOKSON ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claim 10-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11. An action on the merits of claims 1-9 is set forth below.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

2. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Given the lack of nexus between the preamble of claim 1 and the final positive step, it is unclear whether claim 7 further limits claim 1 as claim 1 already recites the presence of the D13S273*4 allele.

Claim Rejections - 35 USC § 112

Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to a method of diagnosing an individual as being atopic or having a predisposition to atopy wherein the method comprises demonstrating the presence or absence of an allele associated with atopy, wherein the allele is situated at a locus in a region of chromosome 13 up to 1 megabase in length wherein the region contains the locus D13S273. The claims are also seem to be drawn to detecting predisposition to asthma by detecting the presence of D13S273*4.

The claims encompass diagnosing an individual as being atopic or having a predisposition to atopy by demonstrating either the presence or absence of any allele associated with atopy wherein the allele is situated at a locus in a region of chromosome 13 up to 1 megabase in length wherein the region contains the locus D13S273. Such claims cover a research project requiring extensive trial and error analysis, the results of which are unpredictable. The region encompassed by the claims is very large, containing a large number of possible genes and alleles that may or may not be associated with atopy, the identity of which the specification does not teach or describe. Such "alleles" encompass variants or mutants with loss of or altered functions of unknown, uncharacterized genes, whose association to atopy has not been demonstrated or described by the specification. The specification only teaches testing a single allele within this large region, and the results of such a study appear to be conflicting (detailed more fully below). The claims require analysis of a large region that can be up to a

megabase on one side of the locus D13S273, containing unknown, uncharacterized genes and alleles.

The specification teaches that linkage disequilibrium occurs over 50-500 kb of DNA, however the claims do not require that the locus D13S273 be in the middle of the region that contains the unknown, uncharacterized allele, therefore the claims actually encompass a region up to 2 megabases. Regardless of such, that is, even if the region covered only 1 megabase, or even 50-500 kilobases, the specification has not the identity of any atopy associated alleles within this large region. With regard to the likelihood that an atopy gene exists 500 kilobases on either side of D13S273, the art teaches that linkage disequilibrium analysis can lead to false positives because of factors such as population stratification (March, R. Molecular Biotechnology, vol. 13, pp 113-122; see p. 116, col. 2). March teaches that because of such, linkage disequilibrium mapping is often used to fine-map a disease gene when a region of interest has already been mapped (for instance, the cystic fibrosis gene). In the instant case, the specification does not teach of any specific genes or alleles associated with asthma or atopy in this large region, except for D13S273*4 whose asserted association to atopy is unclear. While it is noted that the study in the specification used the transmission disequilibrium test, it is unclear how the results of such a test have associated any allele or gene in this large uncharacterized region with either atopy or asthma. Further, the D13S273*4 allele is drawn to a microsatellite repeat allele, which March teaches (p. 118-119, bridging para) is less suitable for fine mapping or association analysis. March teaches that the large number of alleles becomes a problem when using haplotype based methods, are not usually intragenic, and may have relatively high variable

mutation rates which may destroy linkage disequilibrium between a marker and disease mutation.

The specification teaches a study which tested the association between atopy phenotypes and the single allele D13S273*4. The results taught in the specification are unclear however. The specification recites "the results indicate that D13S273*4 shows a strong reproducible association with atopy in two diverse panels of subjects..." (p. 9) however, it is unclear if the "strong reproducible association" is statistically significant such that the skilled artisan would be able to determine a predictable correlation with regard to diagnosis or detecting a predisposition to atopy and the presence of the marker D13S273*4 in an individual, or the presence or absence of any allele within 1 megabase of D13S273*4. It is unclear from the table on page 8 of the specification, what the p value of .0081 for panel A and p=.0099 for panel B corresponds to. It appears that such corresponds to maternal subjects or alleles, however if this is the case, the values for paternal subjects or alleles are presumed to be non significant given the teachings in the table. If this is the case, the specification appears to teach conflicting associations for atopy phenotypes with D13S273*4, let alone any allele within 1 megabase of D13S273. Further, it is unclear how many alleles or subjects from the total of 80 nuclear families for panel A and 77 extended families for Panel B, were included in the results for the table.

With regard to the claims being drawn to detecting an association between a predisposition to asthma in an individual and the presence of the D13S273*4 allele, the specification does not teach a study which tested the association between D13S273*4 or any allele contained in a region up to 1 megabase, said region containing the locus D13S273. The specification only teaches a study which examined atopy phenotypes, however the specification

teaches at page 1 that "not all asthmatics are atopic and most atopic individuals do not have asthma". Given such teaching, the skilled artisan would not be able to establish a predictable correlation between atopy phenotypes and asthma.

The art is silent as to an association between D13S273*4, and asthma or atopy in individuals. Given this lack of teaching, the art does not overcome the deficiencies in the specification. With regard to any atopy associated allele within this large region, Anderson et al (European Journal of Human Genetics, vol. 10, pp 266-270, 2002) teach genetic analysis of the 13q14 region of chromosome 13. Anderson teaches that seven novel microsatellites were recovered and that the most significant association to the serum IgE in the primary dataset was to the novel microsatellite USAT24G1 (see p. 269, col. 2, 3rd full para). However, Anderson does not teach the identity of an atopy gene in this region. (col. 2, para. 4 and 5). Additionally, Anderson teaches the need for further experimentation. Anderson teaches the statistical significance of the weak associations of IgE levels to other microsatellites in the 200 kb USAT24G1-D13S273 interval is uncertain and indicates that the entire interval should be investigated with a dense SNP map, and for the comprehensive characterization of all transcripts. The teachings of Anderson illustrate the extensive trial and error experimentation that would be required for the skilled artisan to practice the invention given the teachings of the specification. Given this post filing teaching, the skilled artisan would not have been able to establish that the specification, at the time of filing, established a predictable correlation as to the identity of atopy associated alleles within the large region encompassed by the claims.

Therefore, given the lack of a teaching of a predictable correlation between atopy phenotypes and D13S273*4, or any allele contained in a region up to 1 megabase containing the

locus D13S273, or between a predisposition to asthma and D13S273*4, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. Firstly, neither the art nor the specification have established a correlation between D13S273*4 and asthma. As the specification states that not all asthmatics are atopic and most atopic individuals do not have asthma, the results in the specification do not establish a predictable correlation between atopy phenotypes and asthma. The skilled artisan would be required to establish whether such a correlation could be made with regard to D13S273*4 and asthma, based on the results in the specification as well as the unpredictability taught in the specification. Secondly, the claims broadly encompass diagnosing atopy or a predisposition to atopy based on either the presence or absence of any allele in a very large region that contains a large number of genes and alleles that have not been identified or characterized or associated with atopy. This recitation covers a research project requiring trial and error analysis, the results of which are unpredictable. In addition the results presented for evidence of an association between D13S273*4 appear to be conflicting, and do not establish a predictable correlation between the presence of the allele and either a predisposition to or diagnosis of atopy in an individual.

Written Description

5. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass diagnosing an individual as being atopic or having a predisposition to atopy by demonstrating either the presence or absence of an allele associated with atopy wherein the allele is situated at a locus in a region of chromosome 13 up to 1 megabase in length wherein the region contains the locus D13S273. However, the specification has not taught or described any genes or alleles (other than D13S273*4) in this large region, let alone any associated with atopy. The specification only teaches testing a single allele within this large region (D13S273*4), and the results of such a study appear to be conflicting (detailed more fully below). The claims require analysis of a large region that can be up to a megabase on one side of the locus D13S273, containing unknown, uncharacterized genes and alleles, which have not been taught or described in the specification. For example, Anderson et al (p. 269, col. 2, 3rd full para) teach a novel microsatellite marker USAT24G1 which appears to be associated with serum IgE, however the identity of such was not taught or described in the specification. Further, Anderson demonstrates that the identity of such putative atopy associated alleles is unknown by teaching that the 200kb USAT24G1-D13S273 interval should be investigated with a dense SNP map and for the comprehensive characterization of all transcripts (co. 2, 5th para). Neither the specific structure, nor specific location of the alleles encompassed by the claims are taught or described in the specification, and the claimed invention only identifies this large number of possible alleles by their function (association to atopy). The specification does not describe this large number of unknown alleles such that the structure of such alleles would be apparent by their function. Further, with regard to claim 9, the identification of such alleles is carried out by sequences whose structures themselves are undefined. The specification does not

define what is encompassed by "substantially similar", and therefore, the structure of these sequences cannot be envisioned.

The specification teaches a study which tested the association between atopy phenotypes and the single allele D13S273*4. The results taught in the specification are unclear however. The specification recites "the results indicate that D13S273*4 shows a strong reproducible association with atopy in two diverse panels of subjects..." (p. 9) however, it is unclear if the "strong reproducible association" is statistically significant such that the skilled artisan would be able to determine a predictable correlation with regard to diagnosis or detecting a predisposition to atopy and the presence of the marker D13S273*4 in an individual, or the presence or absence of any allele within 1 megabase of D13S273*4. It is unclear from the table on page 8 of the specification, what the p value of .0081 for panel A and p=.0099 for panel B corresponds to. It appears that such corresponds to maternal subjects or alleles, however if this is the case, the values for paternal subjects or alleles are presumed to be non significant given the teachings in the table. If this is the case, the specification appears to teach conflicting associations for atopy phenotypes with D13S273*4, let alone any allele within 1 megabase of D13S273.

The disclosure of the single allele D13S273*4, whose association to atopy is unclear, is not representative of the extremely large number of possible alleles which could be located up to 1 megabase (or even 50-500 kilobases) of D13S273, which are associated with atopy. The specification does not demonstrate a correlation or association between any of these unknown, uncharacterized alleles and atopy. The structure or specific location of these alleles are not taught or described. Further, were an association between D13S273*4 and atopy shown, this

single allele would not be representative of the hundreds of uncharacterized, unknown alleles, that would be encompassed by the claimed method.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Based on the lack of teaching or description of a representative number of atopy associated alleles within the extremely large region of DNA recited in the claims, the skilled artisan cannot envision the detailed chemical structure of the encompassed alleles. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. It is noted that the instant claims are drawn to methods, however, the methods require the identification of uncharacterized, unknown alleles that have not been taught or described in the specification.

Consequently, the specification fail to provide adequate written description of the invention of claims 1-9.

Indefinite

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite as the final process step does not relate back to the preamble. The preamble states a method for diagnosing an individual as being atopic or as having a predisposition to atopy but the final process step states that the presence of the D13S273*4 allele is indicative of a predisposition to asthma. Consequently, it cannot be determined if the method is drawn to diagnosing atop, detecting a predisposition to atopy, or to detecting a predisposition to asthma. Further, it is unclear if the method is drawn to detecting the presence or absence of any allele situated at a locus in a region of chromosome 13 of up to 1 megabase in length wherein the region contains the locus D13S273 (as stated in the body of the claim) or whether the method is drawn to detecting a specific allele, D13S273*4 (as stated in the last positive step of the claim). Further, due to the lack of nexus between the preamble of the claim and the last positive step, it is unclear if the method is a screening method (that is just drawn to detecting the presence or absence of an allele-as stated in the body of the claim), or if the claim establishes a correlation between the presence of an allele and a disease (asthma or atopy) or the absence of an allele and a disease (asthma or atopy). It is further unclear how the absence of an atopy associated allele is indicative of atopy. The claim is wholly indefinite, and it cannot be determined what the method steps involve, or what the method is drawn to. Consequently, the metes and bounds of the claims are unclear.

Claim 7 is indefinite as it is unclear if the claim is intended to further limit claim 1. Claim 1 contains the limitation in the last positive step that the allele is D13S273*4. Further, it

is unclear what is being identified with regard to claim 7, diagnosis of atopy, predisposition to atopy, or predisposition to asthma?

Claim 9 is indefinite as it is unclear what is meant by "substantially similar sequences". The specification does not define this term and therefore the structure of the resulting nucleic acids is unclear. Further, it is unclear if the recitation of "identified" encompasses the exact sequence of SEQ ID NOS 1 and 2, or if the recitation encompasses sequences of variable complementarity to SEQ ID NOS 1 and 2.

Conclusion

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
Jehanne Souaya
3/19/03